Influence of Nitric Oxide and Angiotensin II on Renal Involvement in Hypertension

Edward D. Frohlich

Abstract Remarkable advances have been made with prolonged antihypertensive therapy in reversing cardiovascular morbidity and mortality. Deaths from stroke have been reduced by 70% and from coronary heart disease by 35%. In contrast, end-stage renal disease resulting from hypertension continues to increase. The explanations for this seeming paradox remain unresolved even though experimental models have demonstrated that certain antihypertensive agents may have beneficial renal and intrarenal hemodynamic effects, but reversal of the intrarenal pathological lesions has not been shown to improve. This discussion summarizes recent studies from our laboratory in aged (73- and 85-week-old) spontaneously hypertensive rats (SHR) with naturally occurring end-stage renal disease and in a model of aged SHR employing nitric oxide inhibition in younger, adult (20-week-old) SHR. Our findings demonstrated that the systemic and whole renal hemodynamics, intrarenal glomerular dynamics, proteinuria, and renal pathological lesions can be prevented or reversed with angiotensin-converting enzyme inhibition therapy but not with hydrochlorothiazide (at similar levels of arterial pressure reduction). The implications and possible mechanisms involved in the development of both naturally occurring and nitric oxide-exacerbated SHR are multifactorial, involving the endothelial nitric oxide system and its interaction with angiotensin II (and possibly bradykinin) among other factors. Moreover, these pathophysiological cellular mechanisms may be shared by the aging process as well as in naturally occurring spontaneous hypertension in the rat and, perhaps, in humans with essential hypertension. Thus, antihypertensive therapy seems to be specific in its ability to prevent and even reverse the pathophysiological derangements of renal involvement in hypertension. Thus, prevention and reversal of end-stage renal disease do not seem to require greater reduction of arterial pressure than with other target-organ involvement. However, they do require specific inhibition of the arteriolar and glomerular lesions produced by the disease (Hypertension, 1997;29[part 2]:188-193.)

Key Words: endothelium • glomerular disease • arteriolar disease • L-NAME • nitric oxide • L-arginine • angiotensin-converting enzyme inhibition • nephrosclerosis • hydrochlorothiazide

Renal Involvement in Hypertension

The remarkable effects of antihypertensive drug therapy on the reversal of target-organ involvement from hypertension is a classic success story in hypertension. Outcome analyses have clearly demonstrated the remarkable effects of prolonged antihypertensive therapy on reducing the morbidity and mortality of hypertensive vascular disease from stroke and coronary heart disease. Not usually commented upon in this context, at least as a follow-up thought, is the additional well-known observation that as the foregoing dramatic reductions in deaths from stroke (by upwards of 70%) and from coronary heart disease (by 35%) have continued, there has been an unrelenting increase in the numbers of patients with hypertension progressing to ESRD. This is a tremendously disturbing statistic, and it is all the more unsatisfying because it leaves hypertension researchers (fundamental as well as clinical) without a satisfying explanation for this devastating and costly world-wide observation that, at present, defies explanation.

Nephrologists concerned with this seeming paradox have thus far provided no credible rationale for the continued rise in patients with ESRD (Fig 1), although several tentative explanations have been offered. Among these reasonable hypotheses are: target-organ involvement of the kidney by hypertensive vascular disease may not necessarily be reversible with antihypertensive therapy, goal treatment BPs conventionally chosen for antihypertensive therapy (ie, <140 and 90 mm Hg, systolic and diastolic, respectively) may not be optimal and low enough to affect the kidney beneficially, and the antihypertensive...
thorough clinical trials that have demonstrated reductions in morbidity and mortality from stroke and coronary heart disease were not specific enough for the kidney. Supporting these contentions are the unavailing long-term epidemiological data of the past 20 years. This is not to say that every patient progressing into ESRD does so from long-standing essential hypertension; but the vast majority of patients are hypertensive and are either black or have coexisting diabetes mellitus (Fig 2).

Background Experimental Studies

In recent years, a number of experimental models have been developed for producing ESRD. In brief, they have usually involved induction of renal failure with unilateral nephrectomy and extirpation of contralateral renal tissue or with additional salt loading, steroid administration, renal infarction, or administration of nephrotoxic drugs or chemicals. None of these studies, however, have involved the natural development of renal failure in animals with genetic hypertension. Clearly, and of great clinical relevance, these models cannot be considered to be analogous to the patient with essential hypertension who progresses slowly (or even, on rarer occasions, rapidly) into chronic renal failure.

Despite this rather frustrating picture, these studies have led to a very useful hypothesis of the potential dynamics that might be involved with the help of carefully performed renal micropuncture analyses. Thus, these models of hypertension and renal disease have demonstrated that the renal involvement in hypertension is associated with both afferent and efferent glomerular arteriolar constriction, glomerular hypertension and hyperfiltration, leakage of protein molecules across the glomerular capillary wall, progressive glomerulosclerosis, and ultimately renal functional deterioration.

In our earlier micropuncture studies involving the 20- to 23-week-old male SHR, we demonstrated abnormal responsiveness of the SHR afferent and glomerular arterioles to \( \alpha \)-adrenergic stimulation and inhibition as well as to improve renal and glomerular dynamics after acute or prolonged administration of a calcium antagonist or an ACE inhibitor. However, these relatively younger SHR did not exhibit any evidence of increased efferent arteriolar resistance, elevated glomerular hydrostatic pressure, or proteinuria, which had been postulated earlier. Therefore, armed with the knowledge that when the SHR becomes 1 year old, it naturally develops marked proteinuria and impaired renal excretory function that is associated with pathological evidence of glomerular injury, we embarked on a series of studies that provide the substance of this lecture. But, before describing those studies, a word is necessary concerning the rationale for this protocol.

Over the past 15 or so years, we had reported a series of studies on another target-organ involvement from hypertension—the pharmacological reversal of increased left ventricular mass in the SHR. Each of those studies involved the intervention of a pharmacological agent for a period of 3 weeks in male, adult SHR 20 to 23 weeks old. Those studies demonstrated from the outset that certain classes of pharmacological agents for 3 weeks were sufficient to reduce left ventricular mass. Most important, we had selected the 3-week period of treatment because we had postulated earlier that participating in the development and reversal of left ventricular hypertrophy (LVH) were nonhemodynamic and hemodynamic factors. If early reversal of LVH were demonstrated, it would be likely to be independent of hemodynamic factors of pressure and afterload reduction. Thus, the following studies concerned with renal involvement in hypertension were similarly designed to determine whether antihypertensive therapy for 3 weeks would be effective in reversing the renal pathological lesions as well as the associated hemodynamic and micropuncture glomerular dynamic defects.

The SHR: A Model of Renal Involvement in a Genetic Form of Hypertension

Naturally Occurring ESRD

Having been satisfied that changes associated with naturally occurring ESRD do, in fact, occur in the SHR, we set aside a number of adult, male, 20-week-old SHR to age for 1 additional year after our usual study age of 20 weeks. This would permit us to determine whether the systemic and renal hemodynamics as well as glomerular dynamic changes could be associated with that period of aging. These studies clearly demonstrated that by 73 weeks of age, the SHR (in contrast to its normotensive Wistar-Kyoto control of the same age and sex) developed severe glomerular hypertension and ischemia associated with marked afferent and efferent arteriolar constriction, glomerular sclerosis and arteriolar fibrinoid necrosis, and severe proteinuria. Moreover, an equal number of male littermates of these aged SHR, when treated with the same ACE inhibitor used earlier in younger SHR, significantly reversed these marked systemic and renal hemodynamic and glomerular dynamic alterations, as well as the associated pathological lesions and the severe proteinuria within the 3-week treatment.

L-NAME Model for the 73-Week-Old SHR

Having demonstrated that naturally occurring hypertensive ESRD did in fact occur in the aged SHR, we then...
determined whether the changes affected by the additional year of aging could be accelerated by 3 weeks of NO synthase enzymatic inhibition. NO had been shown earlier to be the major source of the endothelium-derived relaxing factor that plays a critical role in local circulatory control, even in the kidney. Moreover, other studies had shown that responses to endothelium-dependent vasodilators were impaired in the SHR, possibly the result of reduced endothelium-derived NO or increased endothelium-derived constricting factor. We therefore determined whether inhibition of the synthesis of endothelium-derived NO in the 20- to 23-week-old SHR might mimic the findings that we had demonstrated in the aged SHR with naturally developing ESRD. To test this hypothesis, we inhibited the synthesis of endothelium-derived NO with L-NAME for 3 weeks (50 mg/L drinking water prepared freshly each day). These studies demonstrated that the L-NAME produced marked proteinuria associated pathologically with severe hypertensive nephrosclerosis that was manifested physiologically by intense afferent glomerular arteriolar constriction with severe afferent arteriolar fibrinoid necrosis, segmental glomerular hyalinosis and sclerosis, and renal ischemia. Significant afferent glomerular arteriolar constriction was also produced but occurred without development of glomerular hypertension because of the more intense afferent arteriolar constriction that was associated with a significantly reduced renal blood flow and single nephron plasma flow. Thus, the 3-week intervention period with L-NAME mimicked the renal and intrarenal hemodynamic and glomerular dynamic alterations as well as the pathological and proteinuric findings we had observed earlier in the 73-week-old SHR (Figs 3 through 6).

**Pharmacological Interventions**

Next, it was of interest to know whether treatment with the same ACE inhibitor that we had used in the earlier two studies would reverse the renal alterations that were associated earlier with L-NAME. To accomplish this, the same ACE inhibitor was administered either for 3 weeks contemporaneously with the L-NAME (a prevention intervention) or after the 3-week L-NAME treatment (a reversal intervention). These studies demonstrated that the cotreatment as well as the posttreatment with that ACE inhibitor did in fact produce equivalent reductions in arterial pressure and total peripheral resistance that were associated with significant decreases in both afferent and efferent arteriolar resistances, nephrosclerosis pathologic scores (of both the glomeruli and the arterioles), and 24-hour urinary protein excretion. Most notably, ACE inhibition cotreatment with L-NAME completely prevented the renal glomerular hemodynamic alterations associated with L-NAME, and when it was given immediately after the L-NAME, it also reversed the glomerular injury scores that were observed in the same SHR earlier by renal biopsy following L-NAME. These changes were also associated with reduced smooth muscle α-actin deposition (by immunohistochemistry). Thus, these data demonstrated that ACE inhibition not only prevented but also reversed the L-NAME-exacerbated severe nephrosclerosis in the SHR, as indicated by improved systemic and

**Percent Distribution of Incidence Counts for Selected Diagnoses, 1990-1992**

![Chart showing the percent distribution of incidence counts for selected diagnoses, 1990-1992.](chart)

**Fig. 2.** Identified causes of ESRD in the United States clearly showing that diabetes mellitus and hypertension are the first two diseases that are most common (with permission).

**Systemic Hemodynamics in SHR**

![Systemic hemodynamic responses of 23-week-old male SHR that were untreated (open bars), given L-NAME (50 mg/L) in drinking water (open crosshatched bars), given L-NAME with an ACE inhibitor (ACEI) (stippled bars), or given L-NAME with hydrochlorothiazide (HCTZ) by gavage (closed crosshatched bars) for 3 weeks. All bars represent mean ± 1 SEM. TPRI indicates total peripheral resistance index. **P < 0.05 vs control; tP < 0.05 vs L-NAME; and ×P < 0.01 vs ACEI.](chart)

**Fig. 3.** Systemic hemodynamic responses of 23-week-old male SHR that were untreated (open bars), given L-NAME (50 mg/L) in drinking water (open crosshatched bars), given L-NAME with an ACE inhibitor (ACEI) (stippled bars), or given L-NAME with hydrochlorothiazide (HCTZ) by gavage (closed crosshatched bars) for 3 weeks. All bars represent mean ± 1 SEM. TPRI indicates total peripheral resistance index. **P < 0.05 vs control; tP < 0.05 vs L-NAME; and ×P < 0.01 vs ACEI.

**Glomerular Dynamic Responses in SHR**

![Glomerular dynamic responses of 23-week-old male SHR that were untreated (open bars), given L-NAME (50 mg/L) in drinking water (open crosshatched bars), given L-NAME with an ACE inhibitor (ACEI) (stippled bars), or given L-NAME with hydrochlorothiazide (HCTZ) by gavage (closed crosshatched bars) for 3 weeks. All bars represent mean ± 1 SEM. SNPF indicates single-nephron plasma flow; SNFF, single-nephron glomerular filtration rate; SNF, single-nephron filtration fraction; and Kf, glomerular filtration coefficient. **P < 0.05 vs control; tP < 0.05; tP < 0.01 vs L-NAME; ×P < 0.05; ×P < 0.01 vs ACEI.](chart)
renal hemodynamic, glomerular dynamic, proteinuric, and pathological alterations.\(^{36}\)

In contrast to the foregoing findings with the ACE inhibitor were our very recent observations with the daily administration (by gastric gavage) of hydrochlorothiazide (HCTZ) for 3 weeks following the 3-week L-NAME period of treatment.\(^{37}\) In these studies, the diuretic achieved a reduction in arterial pressure similar to that produced by the ACE inhibitor; however, renal micropuncture studies revealed an increased glomerular capillary pressure that was associated with a further increase in efferent (but unchanged afferent) glomerular arteriolar resistance as compared with the L-NAME control SHR group. Furthermore, the thiazide diuretic significantly increased the glomerular injury score further (without affecting the arteriolar injury score) that was also associated with a further increase in urinary protein excretion. The pathological studies showed further that the increased glomerular hydrostatic pressure was associated with more severe nephrosclerosis associated with increased fibrotenin and smooth muscle \(\alpha\)-actin deposition. Thus, our pharmacological studies clearly demonstrated that whereas an ACE inhibitor could prevent exacerbation of the renal disease, since a local renin-angiotensin system is involved,\(^{39-44}\) our findings in the SHR seem to favor the concept that progression of the disease (Figs 3 through 6).\(^{37}\)

To provide further insight into the underlying mechanisms that could be involved with these changes, we administered L-arginine (2 g/L drinking water) for 3 weeks to 85-week-old male SHR (not given L-NAME). Although these data have not yet been published, they have been presented at this meeting of the Council.\(^{38}\) The data demonstrated that the 3-week course of L-arginine treatment markedly reversed the severe naturally occurring nephrosclerosis in these rats as well as the cardiac and renal hemodynamic alterations. Although the mean arterial pressure did not remain reduced to levels that were observed earlier with an intravenous infusion of L-arginine (300 mg/kg body wt over 30 minutes) during the baseline, control study period, the acute intravenous response was restored after the 3-week oral treatment by a repeat intravenous infusion of L-arginine. Moreover, the 3-week treatment period significantly improved the glomerular arteriolar injury score (but not arteriolar injury) while reducing the proteinuria.

**Interpretation of the SHR Findings**

The results of these studies strongly support the following three concepts. First, reversibility of ESRD secondary to naturally developing hypertension (or, for that matter, in L-NAME–exacerbated hypertension) in the SHR is possible with antihypertensive therapy. Second, the reversibility of systemic and renal hemodynamic as well as glomerular dynamic, pathological, and proteinuric alterations were not necessarily dependent on dramatic reductions in systolic or diastolic pressure any more than with other target-organ involvement. And third, the demonstrated pathological reversibility seems to be more dependent on the mechanism of action of the antihypertensive drug or drugs employed and can be achieved in as short a time period as 3 weeks in the SHR. Indeed, this relatively short-term reversibility had been shown earlier with the reduction of left ventricular mass (in the SHR), which pointed to the locally mediated nonhemodynamic mechanisms of the antihypertensive drugs.\(^{23-24}\) Thus, whether in the naturally occurring hypertension of the aged SHR or in the exacerbated hypertensive disease produced by NO inhibition in the endothelium of younger, but adult, SHR, impairment of the generation of Ang II (eg, with an ACE inhibitor) seemed to favor that reversibility.\(^{26,38}\) In contrast, the thiazide diuretic, which enhances generation of Ang II through its stimulation of the renin-angiotensin system,\(^{29}\) exacerbated the pathophysiological alterations of the renal disease. Since a local renin-angiotensin system seems to exist within the kidney,\(^{40-42,44}\) our findings in the SHR seem to favor the concept that progression of the disease is mediated locally.

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**Fig 5. Intrarenal hemodynamic responses of 23-week-old male SHR that were untreated (open bars), given L-NAME (50 mg/L) in drinking water (open crosshatched bars), given L-NAME with an ACE inhibitor (ACEI) (stippled bars), or given L-NAME with hydrochlorothiazide (HCTZ) by gavage (closed crosshatched bars) for 3 weeks. All bars represent mean±1 SEM. PG indicates glomerular pressure; SFP, stop-flow pressure; \(R_a\), afferent glomerular arteriolar resistance; and \(R_e\), efferent glomerular arteriolar pressure. **\(P<.01\) vs control; \(\dagger P<.01\) vs L-NAME; \(\ddagger P<.05\), \(\gg\gg P<.01\) vs ACEI.

**Fig 6. Urinary protein excretion (\(U_{\text{proV}}\)) in 24 hours and pathological changes in 23-week-old male SHR that were untreated (open bars), given L-NAME (50 mg/L) in drinking water (open crosshatched bars), given L-NAME with an ACE inhibitor (ACEI) (stippled bars), or given L-NAME with hydrochlorothiazide (HCTZ) by gavage (closed crosshatched bars) for 3 weeks. All bars represent mean±1 SEM. \(GIS+\text{AIS}\) indicates glomerular injury score plus arteriolar injury score. **\(P<.01\) vs control; \(\dagger P<.05\), \(\ddagger P<.01\) vs L-NAME; \(\gg\gg P<.01\) vs ACEI.
hypertensive glomerular disease occurs in association with generation of Ang II despite a reduction of systemic arterial pressure similar to that which was also achieved by the ACE inhibitor.\(^{30,37}\)

Our experimental data at the least provide some tentative mechanistic explanations for the rise of ESRD in predisposed patients with hypertension who may be particularly susceptible to diuretic therapy. Nevertheless, it may not be appropriate at this time to suggest with firm conviction that Ang II was the sole pathogenetic factor responsible for the progression of the hypertensive renal disease since ACE inhibition alone or with NO interaction may also involve other local mechanisms such as the local generation of kinins or the secondary effects on other endothelium-derived factors in the kidney and elsewhere.\(^{31,35,49-51}\) To this end, our studies involving the inhibition of endothelially generated NO may also be co-participants in the pathophysiological responses reported herein. Sufficient data are now available to support the thesis of a locally functioning renin-angiotensin system that may interact with an NO synthase-dependent system or other related endothelium-generated mechanisms.

That aging, per se, of the SHR may be analogous to suppression of the endothelium-derived generation of NO is supported by several lines of evidence. Thus, NO synthesis seems to be impaired in experimental animals and humans with aging\(^{52,53}\) as well as secondarily in endothelium-related diseases such as hypercholesterolemia and atherosclerosis\(^{4,55}\) and essential hypertension.\(^{36-59}\) The present (and highly controlled) studies in the SHR with naturally developing hypertensive ESRD (or with L-NAME-exacerbated ESRD in the younger SHR) provide strong support for these potential mechanisms, and ongoing studies are being directed toward these concepts in our laboratory.

It is appropriate in this lecture to honors Arthur Corcoran and the investigative team that offered the multifactorial mechanistic explanation of hypertension (the "mosaic" of hypertension)\(^{40}\) to suggest a similar mechanism for the underlying factors associated with ESRD (Fig 7).

As with the causation of hypertension, this mosaic is not exhaustive but involves the interaction of other pathophysiological processes including those of the aging process, atherosclerosis, and diabetes mellitus. It also involves those specific factors related to race, growth, immune responses, and lipid metabolism as well as with the generation of NO, Ang II, free radicals, and other humoral and therapeutic agents.

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